EXHIBIT A

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(54) **SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS**

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(63) Continuation of application No. 11/367,238, filed on Mar. 3, 2006, now abandoned.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

38 Claims, No Drawings

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. application Ser. No. 11/367,238, filed Mar. 3, 2006, which is related to and claims priority under 35 U.S.C. §119(e) to U.S. provisional patent application U.S. Ser. No. 60/659,679 entitled "Solvent System for Enhancing the Solubility of Pharmaceutical Agents", filed Mar. 8, 2005. The entire contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent

Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al. discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Option-

ally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85

-continued

Ingredients	% (by weight)
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00

-continued

Ingredients	% (by weight)
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A pharmaceutical composition comprising soft gelatin capsule comprising a fill material comprising:

(a) a naproxen salt;

(b) about 5% lactic acid by weight of the fill material; and

(c) polyethylene glycol.

2. The composition of claim **1**, wherein polyethylene glycol comprises about 10% to about 80% by weight of the fill material.

3. The composition of claim **1**, wherein the polyethylene glycol comprises one or more polyethylene glycols comprising molecular weights between 300 and 1500.

4. The composition of claim **1**, further comprising one or more excipients.

5. The composition of claim **4**, wherein the excipients comprise plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, or combinations thereof.

6. The composition of claim **1**, further comprising a solubilizer selected from glycerin, polyvinylpyrrolidone, propylene glycol, or a combination thereof.

7. The composition of claim **6**, wherein the solubilizer is present in amount from about 1% to about 10% by weight of the fill material.

8. A method of making the composition of claim **1**, the method comprising the steps of:

(i) mixing the naproxen salt, lactic acid, and polyethylene glycol at an appropriate temperature to form a fill material; and

(ii) encapsulating the fill material in a soft gelatin capsule.

9. The method of claim **8**, wherein the appropriate temperature is from about 50° C. to about 70° C.

10. A soft gelatin capsule comprising a fill material, the fill material comprising:

(a) a naproxen salt;

(b) about 5% lactic acid by weight of the fill material; and

(c) polyethylene glycol.

11. The capsule of claim **10**, wherein polyethylene glycol comprises about 10% to about 80% by weight of the fill material.

12. The capsule of claim **10**, wherein the polyethylene glycol comprises one or more polyethylene glycols comprising molecular weights between 300 and 1500.

13. The capsule of claim **10**, further comprising one or more excipients.

14. The capsule of claim **13**, wherein the excipients comprise plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, or combinations thereof.

15. The capsule of claim **10**, further comprising a solubilizer selected from glycerin, polyvinylpyrrolidone, propylene glycol or a combination thereof.

16. The capsule of claim **15**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

17. A method of using the capsule of claim **10** comprising administering to a patient in need thereof an effective amount of the capsule.

18. A soft gelatin capsule comprising a fill material comprising:

(a) about 10% to about 80% by weight of the fill material polyethylene glycol having a molecular weight between 300 and 1500;

(b) about 10% to about 50% by weight of the fill material naproxen sodium; and

(c) about 5% of the fill material lactic acid.

19. A method of using the capsule of claim **18** comprising administering to a patient in need thereof an effective amount of the capsule.

20. A pharmaceutical composition prepared by a method comprising preparing a fill material comprising:

mixing together

(a) a naproxen salt;

(b) about 5% by weight of the fill material lactic acid; and

(c) polyethylene glycol having a molecular weight between 300 and 1500.

21. A soft gelatin capsule prepared by a method comprising:

(a) producing a fill material by mixing:

(i) a naproxen salt;

(ii) about 5% by weight of the fill material lactic acid;

(iii) polyethylene glycol having a molecular weight between 300 and 1500; and

(b) encapsulating the mixture in a soft gelatin capsule.

22. The composition of claim **1**, wherein the naproxen salt comprises sodium naproxen.

23. The composition of claim **6**, wherein the solubilizer comprises polyvinylpyrrolidone.

24. The method of claim **8**, wherein the naproxen salt comprises sodium naproxen.

25. A capsule produced by the method of claim **8**.

26. The capsule of claim **10**, wherein the naproxen salt comprises sodium naproxen.

27. The capsule of claim **15**, wherein the solubilizer comprises polyvinylpyrrolidone.

28. The capsule of claim **18**, wherein the fill further comprises a solubilizer.

29. The capsule of claim **28**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

30. The capsule of claim **28**, wherein the solubilizer comprises polyvinylpyrrolidone.

31. The method of claim **20**, wherein the naproxen salt comprises sodium naproxen.

32. The method of claim **20**, wherein the fill material further comprises a solubilizer.

33. The method of claim **32**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

34. The method of claim **32**, wherein the solubilizer comprises polyvinylpyrrolidone.

35. The capsule of claim **21**, wherein the naproxen salt comprises sodium naproxen.

36. The capsule of claim **21**, wherein the fill material further comprises a solubilizer.

37. The capsule of claim **36**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

38. The capsule of claim **36**, wherein the solubilizer comprises polyvinylpyrrolidone.

* * * * *

EXHIBIT B

US009693979B2

(12) **United States Patent**
Chidambaram et al.

(10) **Patent No.: US 9,693,979 B2**
(45) **Date of Patent: *Jul. 4, 2017**

(54) **LIQUID DOSAGE FORMS OF SODIUM NAPROXEN**

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(60) Provisional application No. 60/659,679, filed on Mar. 8, 2005.

(51) **Int. Cl.**

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A61K 31/765	(2006.01)
A61K 47/12	(2006.01)
A61K 9/50	(2006.01)
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(52) **U.S. Cl.**

CPC ***A61K 31/192*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/4825*** (2013.01); ***A61K 9/4833*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 9/4866*** (2013.01); ***A61K 9/50*** (2013.01); ***A61K 9/5089*** (2013.01); ***A61K 31/765*** (2013.01); ***A61K 47/12*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

19 Claims, No Drawings

LIQUID DOSAGE FORMS OF SODIUM NAPROXEN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 14/977,808, filed on Dec. 22, 2015, which is continuation of U.S. patent application Ser. No. 11/367,238, filed Mar. 3, 2006, which claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/659,679, filed Mar. 8, 2005, each of which are incorporated herein in its entirety by express reference thereto.

TECHNICAL FIELD

This application describes liquid dosage forms of sodium naproxen in soft gelatin capsules.

BACKGROUND

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al.

discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore, it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

SUMMARY

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, such as naproxen, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

One embodiment described herein is a pharmaceutical composition comprising a soft gel capsule encapsulating a liquid matrix comprising: (a) naproxen sodium; (b) one or more deionizing agents comprising fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium; (c) one or more polyethylene glycols; and (d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the deionizing agent comprises

citric acid or lactic acid. In another aspect described herein, the deionizing agent comprises lactic acid. In another aspect described herein, the polyethylene glycol comprises from about 10% to about 80% by weight of the composition. In another aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises from about 1% to 10% by weight of the composition. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

Another embodiment described herein is a pharmaceutical composition comprising: (a) about 25% naproxen sodium by weight; (b) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (c) about 10% to about 80% of one or more polyethylene glycols by weight; and (d) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises propylene glycol and polyvinyl pyrrolidone. In another aspect described herein, the lactic acid comprises about 0.6 mole equivalents per mole of naproxen sodium. In another aspect described herein, the weight percentage of lactic acid is about 5%. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof. In another aspect described herein, the pH is from about 2.5 to about 7.5. In another aspect described herein, the composition is encapsulated in a softgel capsule. In another aspect described herein, the softgel capsule comprises: (a) gelatin; (b) plasticizer; and (c) purified water.

Another embodiment described herein is a method for making a pharmaceutical composition, the method comprising: (a) mixing together (i) about 25% naproxen sodium by weight; (ii) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (ii) about 10% to about 80% of one or more polyethylene glycols by weight; and (iv) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof; and (b) encapsulating the mixture in a softgel capsule using rotary die encapsulation.

Another embodiment described herein is an oral dosage form produced by the method described herein.

DETAILED DESCRIPTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dex-

tromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Compositions

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Methods of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and poly-

ethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Methods of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40
TOTAL	100%

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40
TOTAL	100%

Example 3 Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40
TOTAL	100%

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

-continued

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
TOTAL	100%

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	40.75
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	40.72
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60
TOTAL	100%

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M
Propylene Glycol	2.00
PEG 600	q.s.
TOTAL	100%

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	61.20
PEG 1000	6.80
TOTAL	100%

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	51.00
PEG 1000	17.00
TOTAL	100%

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	34.00
PEG 1000	34.00
TOTAL	100%

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	17.00
PEG 1000	51.00
TOTAL	100%

The invention claimed is:

1. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) naproxen sodium;

(b) about 5% lactic acid by weight of the matrix;

(c) one or more polyethylene glycols; and

(d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof.

2. The composition of claim **1**, wherein the polyethylene glycol comprises from about 10% to about 80% by weight of the matrix.

3. The composition of claim **1**, wherein the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The composition of claim 1, wherein the polyethylene glycol comprises polyethylene glycol 600.

5. The composition of claim 1, wherein the solubilizer comprises from about 1% to 10% by weight of the matrix.

6. The composition of claim 1, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

7. The composition of claim 1, further comprising one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

8. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) about 25% naproxen sodium by weight of the matrix;

(b) about 5% lactic acid by weight of the matrix;

(c) about 10% to about 80% of polyethylene glycol 600 by weight of the matrix; and

(d) about 1% to about 10% of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof by weight of the matrix.

9. The composition of claim 8, wherein the solubilizer comprises propylene glycol and polyvinyl pyrrolidone.

10. The composition of claim 8, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

11. The composition of claim 8, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

12. The composition of claim 8, wherein the matrix further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

13. The composition of claim 8, wherein the matrix comprises a pH from about 2.5 to about 7.5.

14. The composition of claim 8, wherein the soft gelatin capsule comprises:

(a) gelatin;

(b) plasticizer; and

(c) purified water.

15. A method for making the pharmaceutical composition of claim 8, the method comprising:

(a) mixing together the components of 10(*a*) to 10(*d*) to form a mixture; and

(b) encapsulating the mixture in a soft gelatin capsule using rotary die encapsulation.

16. An oral dosage form produced by the method of claim 15.

17. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) about 25% naproxen sodium by weight of the matrix;

(b) about 5% lactic acid by weight of the matrix;

(c) quantum sufficit (q.s.) of polyethylene glycol 600; and

(d) about 1% to about 10% of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof by weight of the matrix.

18. The composition of claim 17, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

19. The composition of claim 17, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

* * * * *

EXHIBIT C

US010022344B2

(12) **United States Patent**
Chidambaram et al.

(10) **Patent No.: US 10,022,344 B2**
(45) **Date of Patent: *Jul. 17, 2018**

(54) **LIQUID DOSAGE FORMS OF SODIUM NAPROXEN**

(71) Applicant: **PATHEON SOFTGELS INC**, High Point, NC (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/817,471**

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Related U.S. Application Data

(63) Continuation of application No. 15/591,512, filed on May 10, 2017, which is a continuation of application No. 14/977,808, filed on Dec. 22, 2015, now Pat. No. 9,693,978, which is a continuation of application No. 11/367,238, filed on Mar. 3, 2006, now abandoned.

(60) Provisional application No. 60/659,679, filed on Mar. 8, 2005.

(51) **Int. Cl.**

A61K 31/192	(2006.01)
A61K 9/48	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/192*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/4825*** (2013.01); ***A61K 9/4833*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 9/4866*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

20 Claims, No Drawings

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Patent Owner's Preliminary Response, IPR2018-00422 (U.S. Pat. No. 9,693,979) May 22, 2018.
Declaration of Mansoor Khan in support of Patent Owner's Preliminary Response, IPR2018-00422 (U.S. Patent No. 9,693,979) May 22, 2018.

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LIQUID DOSAGE FORMS OF SODIUM NAPROXEN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/591,512, filed on May 10, 2017, which is a continuation of U.S. patent application Ser. No. 14/977,808, filed on Dec. 22, 2015, now U.S. Pat. No. 9,693,978, which is continuation of U.S. patent application Ser. No. 11/367,238, filed Mar. 3, 2006, now abandoned, which claims priority under 35 U.S.C. § 119(e) to U.S. Provisional patent application Ser. No. 60/659,679, filed Mar. 8, 2005, each of which is incorporated herein in its entirety by express reference thereto.

TECHNICAL FIELD

This application describes liquid dosage forms of sodium naproxen in soft gelatin capsules.

BACKGROUND

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al. discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore, it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

SUMMARY

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, such as naproxen, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

One embodiment described herein is a pharmaceutical composition comprising a soft gel capsule encapsulating a liquid matrix comprising: (a) naproxen sodium; (b) one or more deionizing agents comprising fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, propionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium; (c) one or more polyethylene glycols; and

(d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the deionizing agent comprises citric acid or lactic acid. In another aspect described herein, the deionizing agent comprises lactic acid. In another aspect described herein, the polyethylene glycol comprises from about 10% to about 80% by weight of the composition. In another aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises from about 1% to 10% by weight of the composition. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

Another embodiment described herein is a pharmaceutical composition comprising: (a) about 25% naproxen sodium by weight; (b) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (c) about 10% to about 80% of one or more polyethylene glycols by weight; and (d) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises propylene glycol and polyvinyl pyrrolidone. In another aspect described herein, the lactic acid comprises about 0.6 mole equivalents per mole of naproxen sodium. In another aspect described herein, the weight percentage of lactic acid is about 5%. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof. In another aspect described herein, the pH is from about 2.5 to about 7.5. In another aspect described herein, the composition is encapsulated in a softgel capsule. In another aspect described herein, the softgel capsule comprises: (a) gelatin; (b) plasticizer; and (c) purified water.

Another embodiment described herein is a method for making a pharmaceutical composition, the method comprising: (a) mixing together (i) about 25% naproxen sodium by weight; (ii) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (ii) about 10% to about 80% of one or more polyethylene glycols by weight; and (iv) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof; and (b) encapsulating the mixture in a softgel capsule using rotary die encapsulation.

Another embodiment described herein is an oral dosage form produced by the method described herein.

DETAILED DESCRIPTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinox-

amine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scopolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, propionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Compositions

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Methods of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Methods of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents, and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40
TOTAL	100%

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40
TOTAL	100%

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85

-continued

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
PEG 400	63.52
Water	7.40
TOTAL	100%

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15
TOTAL	100%

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	40.75
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	40.72
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00

-continued

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
PEG 400	64.64
Water	0.60
TOTAL	100%

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M
Propylene Glycol	2.00
PEG 600	q.s.
TOTAL	100%

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	61.20
PEG 1000	6.80
TOTAL	100%

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	51.00
PEG 1000	17.00
TOTAL	100%

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00

-continued

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
PEG 600	34.00
PEG 1000	34.00
TOTAL	100%

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	17.00
PEG 1000	51.00
TOTAL	100%

The invention claimed is:

1. A soft gelatin capsule comprising a fill material comprising:

(a) naproxen sodium;

(b) about 5% of a deionizing agent comprising acetic acid, propionic acid, pyruvic acid, or lactic acid;

(c) polyethylene glycol; and

(d) a solubilizer comprising glycerin, polyvinylpyrrolidone, propylene glycol, or combinations thereof.

2. The capsule of claim **1**, wherein the deionizing agent is propionic acid or lactic acid.

3. The capsule of claim **1**, wherein the deionizing agent is lactic acid.

4. The capsule of claim **1**, wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of claim **1**, wherein the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of claim **1**, wherein the fill material further comprises water in an amount from 1% to 18% by weight.

7. The capsule of claim **1**, further comprising one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

8. The capsule of claim **1**, wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of claim **1**, wherein the fill material is liquid.

10. A method for treating pain, inflammation, or fever comprising administering the capsule of claim **1** to a patient in need thereof.

11. A method of making the capsule of claim **1** comprising

(a) mixing components (a), (b), (c), and (d) as defined in claim **1**; and

(b) encapsulating the mixture in a softgel capsule.

12. The method of claim **11**, wherein step (a) is conducted at a temperature of from 50° C. to 70° C.

13. A soft gelatin capsule comprising a fill material comprising:

(a) naproxen sodium;

(b) about 5% of a deionizing agent comprising acetic acid, propionic acid, pyruvic acid, or lactic acid;

(c) polyethylene glycol;

(d) a solubilizer comprising glycerin, polyvinylpyrrolidone, propylene glycol, or combinations thereof; and

(e) water.

14. The capsule of claim **13**, wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

15. The capsule of claim **13**, wherein the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500.

16. The capsule of claim **13**, wherein water is present in an amount from 1% to 18% by weight.

17. The capsule of claim **13**, further comprising one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

18. The capsule of claim **13**, wherein the solubilizer is present in amount from 1% to 10% by weight.

19. The capsule of claim **13**, wherein the fill material is liquid.

20. A method for treating pain, inflammation, or fever comprising administering the capsule of claim **13** to a patient in need thereof.

* * * * *

EXHIBIT D

US010028925B2

(12) **United States Patent**
Chidambaram et al.

(10) **Patent No.: US 10,028,925 B2**
(45) **Date of Patent: *Jul. 24, 2018**

(54) **LIQUID DOSAGE FORMS OF SODIUM NAPROXEN**

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(63) Continuation of application No. 14/977,808, filed on Dec. 22, 2015, now Pat. No. 9,693,978, which is a continuation of application No. 11/367,238, filed on Mar. 3, 2006, now abandoned.

(60) Provisional application No. 60/659,679, filed on Mar. 8, 2005.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

23 Claims, No Drawings

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LIQUID DOSAGE FORMS OF SODIUM NAPROXEN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/977,808, filed on Dec. 22, 2015, which is continuation of U.S. patent application Ser. No. 11/367,238, filed Mar. 3, 2006, which claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 60/659,679, filed Mar. 8, 2005, each of which are incorporated herein in its entirety by express reference thereto.

TECHNICAL FIELD

This application describes liquid dosage forms of sodium naproxen in soft gelatin capsules.

BACKGROUND

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al.

discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore, it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

SUMMARY

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, such as naproxen, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

One embodiment described herein is a pharmaceutical composition comprising a soft gel capsule encapsulating a liquid matrix comprising: (a) naproxen sodium; (b) one or more deionizing agents comprising fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, propionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium; (c) one or more polyethylene glycols; and (d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the deionizing agent comprises

citric acid or lactic acid. In another aspect described herein, the deionizing agent comprises lactic acid. In another aspect described herein, the polyethylene glycol comprises from about 10% to about 80% by weight of the composition. In another aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises from about 1% to 10% by weight of the composition. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

Another embodiment described herein is a pharmaceutical composition comprising:

(a) about 25% naproxen sodium by weight; (b) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (c) about 10% to about 80% of one or more polyethylene glycols by weight; and (d) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises propylene glycol and polyvinyl pyrrolidone. In another aspect described herein, the lactic acid comprises about 0.6 mole equivalents per mole of naproxen sodium. In another aspect described herein, the weight percentage of lactic acid is about 5%. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof. In another aspect described herein, the pH is from about 2.5 to about 7.5. In another aspect described herein, the composition is encapsulated in a softgel capsule. In another aspect described herein, the softgel capsule comprises: (a) gelatin; (b) plasticizer; and (c) purified water.

Another embodiment described herein is a method for making a pharmaceutical composition, the method comprising: (a) mixing together (i) about 25% naproxen sodium by weight; (ii) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (ii) about 10% to about 80% of one or more polyethylene glycols by weight; and (iv) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof; and (b) encapsulating the mixture in a softgel capsule using rotary die encapsulation.

Another embodiment described herein is an oral dosage form produced by the method described herein.

DETAILED DESCRIPTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxa-

cin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scopolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, propionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Compositions

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Methods of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel

mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Methods of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40
TOTAL	100%

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40
TOTAL	100%

Example 3 Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40
TOTAL	100%

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15
TOTAL	100%

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	40.75
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	40.72
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60
TOTAL	100%

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M

-continued

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Propylene Glycol	2.00
PEG 600	q.s.
TOTAL	100%

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	61.20
PEG 1000	6.80
TOTAL	100%

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	51.00
PEG 1000	17.00
TOTAL	100%

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	34.00
PEG 1000	34.00
TOTAL	100%

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	17.00
PEG 1000	51.00
TOTAL	100%

The invention claimed is:

1. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:
(a) naproxen sodium;
(b) about 5% lactic acid by weight of the matrix;
(c) one or more polyethylene glycols; and
(d) one or more solubilizers.

2. The composition of claim 1, wherein the solubilizer comprises polyvinylpyrrolidone, propylene glycol, or a combination thereof.

3. The composition of claim 1, wherein the polyethylene glycol comprises from about 10% to about 80% by weight of the matrix.

4. The composition of claim 1, wherein the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500.

5. The composition of claim 1, wherein the polyethylene glycol comprises polyethylene glycol 600.

6. The composition of claim 1, wherein the solubilizer comprises from about 1% to 10% by weight of the matrix.

7. The composition of claim 1, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

8. The composition of claim 1, further comprising one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

9. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:
(a) about 25% naproxen sodium by weight of the matrix;
(b) about 5% lactic acid by weight of the matrix;
(c) about 10% to about 80% of polyethylene glycol by weight of the matrix; and
(d) about 1% to about 10% of one or more solubilizers.

10. The composition of claim 9, wherein the solubilizer comprises polyvinylpyrrolidone, propylene glycol, or a combination thereof.

11. The composition of claim 9, wherein the solubilizer comprises polyvinylpyrrolidone and propylene glycol.

12. The composition of claim 9, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

13. The composition of claim 9, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

14. The composition of claim 9, wherein the matrix further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

15. The composition of claim 9, wherein the matrix comprises a pH is from about 2.5 to about 7.5.

16. The composition of claim 9, wherein the soft gelatin capsule comprises:
(a) gelatin;
(b) plasticizer; and
(c) purified water.

17. A method for making the pharmaceutical composition of claim 9, the method comprising:
(a) mixing together the components of 9(a) to 9(d) to form a mixture; and
(b) encapsulating the mixture in a soft gelatin capsule using rotary die encapsulation.

18. An oral dosage form produced by the method of claim 17.

19. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:
(a) about 25% naproxen sodium by weight of the matrix;
(b) about 5% lactic acid by weight of the matrix;
(c) quantum sufficit (q.s.) of polyethylene glycol; and
(d) about 1% to about 10% of one or more solubilizers.

20. The composition of claim 19, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

21. The composition of claim 19, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

22. The composition of claim 9, wherein the polyethylene glycol comprises polyethylene glycol 600.

23. The composition of claim 19, wherein the polyethylene glycol comprises polyethylene glycol 600.

* * * * *

EXHIBIT E

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

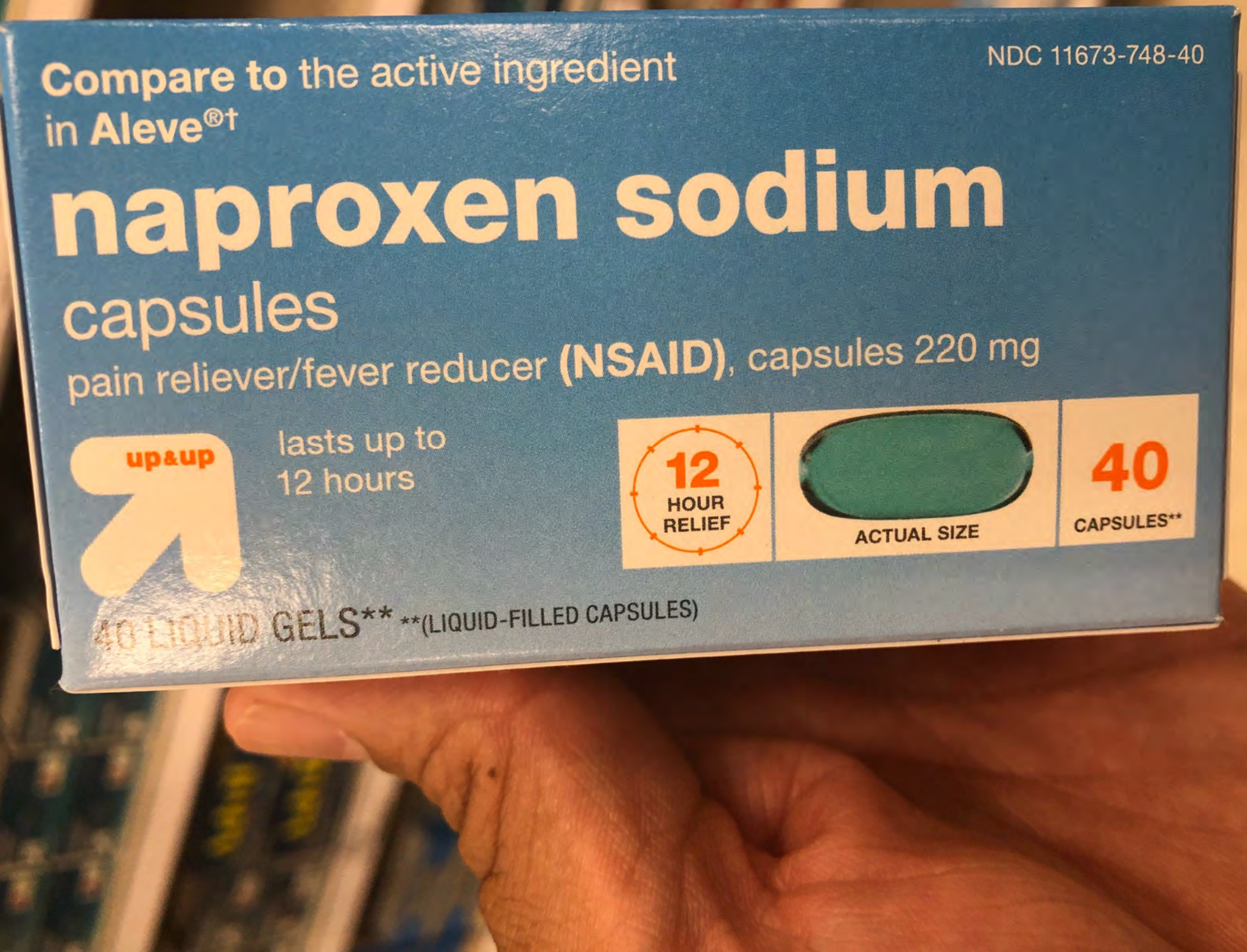
Product Details for ANDA 208363

NAPROXEN SODIUM (NAPROXEN SODIUM)
EQ 200MG BASE

Marketing Status: Over-the-counter

Active Ingredient: NAPROXEN SODIUM
Proprietary Name: NAPROXEN SODIUM
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: EQ 200MG BASE
Reference Listed Drug: No
Reference Standard: No
TE Code:
Application Number: A208363
Product Number: 001
Approval Date: Mar 15, 2018
Applicant Holder Full Name: PURACAP PHARMACEUTICAL LLC
Marketing Status: Over-the-counter
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=208363&Appl_type=A)

EXHIBIT F


Compare to the active ingredient in Aleve®†
NDC 11673-748-40
naproxen sodium
capsules
pain reliever/fever reducer (NSAID), capsules 220 mg
up&up
lasts up to 12 hours
12 HOUR RELIEF
ACTUAL SIZE
40 CAPSULES**
40 LIQUID GELS** **(LIQUID-FILLED CAPSULES)


094 01 0724 R04 ID215478
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Minneapolis, MN 55403
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3 59726 17540 1
PLD-C528A
FC004880
Lot / Exp.: F03937 01/20
Product of: CHINA

EXHIBIT G

Drug Facts

Active ingredient (in each capsule)	Purposes
Naproxen sodium 220 mg (naproxen 200 mg) (NSAID)*	Pain reliever/ fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - minor pain of arthritis
  - backache
  - headache
  - the common cold
  - muscular aches
  - menstrual cramps
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Naproxen sodium may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Drug Facts (continued)

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic
- you have problems or serious side effects from taking pain relievers or fever reducers

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking any other drug

When using this product, take with food or milk if stomach upset occurs.

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
  - chest pain
  - slurred speech
  - leg swelling
  - trouble breathing
  - weakness in one part or side of body
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear
- you have difficulty swallowing
- it feels like the capsule is stuck in your throat

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Drug Facts (continued)

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- drink a full glass of water with each dose
- if taken with food, this product may take longer to work
- adults and children 12 years and older:
  - take 1 capsule every 8 to 12 hours while symptoms last
  - for the first dose you may take 2 capsules within the first hour
  - do not exceed 2 capsules in any 8- to 12-hour period
  - do not exceed 3 capsules in a 24-hour period
- children under 12 years: ask a doctor

Other information

- **each capsule contains:** sodium 20 mg
- store at 20-25°C (68-77°F). Avoid high humidity and excessive heat above 40°C (104°F).
- read all directions and warnings before use. Keep carton.
- swallow whole; do not crush, chew, or dissolve

Inactive ingredients

FD&C blue #1, gelatin, glycerin, lactic acid, lecithin, light mineral oil, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, purified water, shellac glaze, sorbitol sorbitan solution, titanium dioxide, white ink

Questions or comments?

Call **1-800-910-6874**

†This product is not manufactured or distributed by Bayer HealthCare, LLC, distributor of Aleve®.

TAMPER EVIDENT: DO NOT USE IF PRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING.

KEEP OUTER CARTON FOR COMPLETE WARNINGS AND PRODUCT INFORMATION.

EXHIBIT H

NATIONAL DRUG CODES LIST ndclist.com (https://ndclist.com/)

Labeler Index (https://ndclist.com/labeler/index-view-all)
/ Target Corporation (https://ndclist.com/labeler/target-corporation)
/ 11673-748 (https://ndclist.com/ndc/11673-748) / NDC Code: 11673-748-40 Naproxen Sodium

NDC 11673-748-40 NAPROXEN SODIUM

Naproxen Sodium

NDC 11673-748 (https://ndclist.com/ndc/11673-748) Package Codes

Related Codes (https://ndclist.com/ndc/11673-748/related)

NDC PACKAGE CODE 11673-748-40

Field Name	Field Value
NDC Code	**11673-748-40**
Package Description	1 BOTTLE, PLASTIC in 1 BOX > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC
Proprietary Name	**Naproxen Sodium**
Non-Proprietary Name	Naproxen Sodium
11-Digit NDC Billing Format	11673074840
Product Type	Human Otc Drug
Labeler Name	Target Corporation (https://ndclist.com/labeler/target-corporation)
Dosage Form	*Capsule, Liquid Filled* - A solid dosage form in which the drug is enclosed within a soluble, gelatin shell which is plasticized by the addition of a polyol, such as sorbitol or glycerin, and is therefore of a somewhat thicker consistency than that of a hard shell capsule; typically, the active ingredients are dissolved or suspended in a liquid vehicle.
Administration Route(s)	■ Oral - Administration to or by way of the mouth.

Field Name	Field Value
Active Ingredient(s)	■ NAPROXEN SODIUM 220 mg/1 (https://ndclist.com/active-ingredients/naproxen-sodium)
Marketing Category	ANDA - A product marketed under an approved Abbreviated New Drug Application.
FDA Application Number	ANDA208363
Start Marketing Date	04-01-2018

The NDC Code 11673-748-40 is assigned to Naproxen Sodium, a human over the counter drug labeled by Target Corporation. The product's dosage form is capsule, liquid filled and is administered via oral form.

Code Structure

- 11673 - Target Corporation
  - 11673-748 - Naproxen Sodium
    - 11673-748-40 - 1 BOTTLE, PLASTIC in 1 BOX

The NDC Directory contains ONLY information on final marketed drugs submitted to FDA electronically by labelers. A labeler might be a manufacturer, re-packager or re-labeler. The product information included in the NDC directory does not indicate that FDA has verified the information provided by the product labeler. Assigned NDC numbers are not in any way an indication of FDA approval of the product.

* Please review the disclaimer below.

OTHER PRODUCT PACKAGES

The following packages are also available for Naproxen Sodium with product NDC 11673-748.

NDC Package Code	Package Description
11673-748-80 (https://ndclist.com/ndc/11673-748/package/11673-748-80)	1 BOTTLE, PLASTIC in 1 BOX > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC

* Please review the disclaimer below.

Previous Code

< 11673-747 (https://ndclist.com/ndc/11673-747)

Next Code
11673-749 › (https://ndclist.com/ndc/11673-749)

(https://ndclist.com/search-pill-identifier.php)
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Pharmacologic Class Index (https://ndclist.com/pharma-class) | Pill Identification Index (https://ndclist.com/pill-identifier) | NDC - HCPCS Crosswalk (https://ndclist.com/ndc-hcpcs-crosswalk)
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EXHIBIT I

National Drug Code Directory

Current through July 22, 2018

Records marked with (U): This information was removed from publication, because the record is uncertified.

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Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Naproxen Sodium (U)	*33358-259-90*					*RxChange Co.*						*N/A*			*N/A*
NAPROXEN SODIUM DS (U)	*42494-400-01*					*Cameron Pharmaceuticals, LLC*						*N/A*			*N/A*
NAPROXEN SODIUM DS (U)	*42494-400-05*					*Cameron Pharmaceuticals, LLC*						*N/A*			*N/A*
TREXIMET (U)	*21695-954-09*					*Rebel Distributors Corp*						*N/A*			*N/A*

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
CAREALL Naproxen	51824-030-01	220 mg/1	CAPSULE	ORAL	ANDA090545	New World Imports, Inc.	51824-030	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	05/01/2013	N/A	ANDA	100 CAPSULE in 1 BOTTLE, PLASTIC (51824-030-01)	N/A
Naproxen Sodium	69842-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	CVS Pharmacy	69842-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (69842-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	69842-748-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	CVS Pharmacy	69842-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (69842-748-80) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	21130-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Safeway, Inc.	21130-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (21130-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	55301-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	AAFES/Your Military Exchanges	55301-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/28/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (55301-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
NAPROXEN SODIUM	53345-042-01	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Humanwell PuraCap Pharmaceuticals (Wuhan) Co., Ltd	53345-042	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	03/20/2018	N/A	ANDA	1 BAG in 1 BOX (53345-042-01) > 5000 CAPSULE, LIQUID FILLED in 1 BAG	N/A
Naproxen Sodium	41520-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Care One (American Sales Company)	41520-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (41520-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Naproxen Sodium	41520-748-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Care One (American Sales Company)	41520-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (41520-748-80) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	30142-748-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	The Kroger Co.	30142-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	80 CAPSULE, LIQUID FILLED in 1 BOTTLE (30142-748-80)	N/A
Naproxen Sodium	55910-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Dolgencorp, Inc. (DOLLAR GENERAL & REXALL)	55910-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (55910-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	30142-748-12	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	The Kroger Co.	30142-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (30142-748-12) > 120 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	21130-748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Safeway, Inc.	21130-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (21130-748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	30142-748-16	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	The Kroger Co.	30142-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE in 1 BOX (30142-748-16) > 160 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
NAPROXEN SODIUM	51013-137-60	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	PuraCap Pharmaceutical LLC	51013-137	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	03/20/2018	N/A	ANDA	160 CAPSULE, LIQUID FILLED in 1 BOTTLE (51013-137-60)	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Naproxen Sodium	49035-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	EQUATE (Wal-Mart Stores, Inc.)	49035-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (49035-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	46122-534-60	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	AmerisourceBergen (Good Neighbor Pharmacy) 46122	46122-534	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (46122-534-60) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	11673-748-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	TARGET Corporation	11673-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (11673-748-80) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	36800-748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	TOP CARE (Topco Associates LLC)	36800-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (36800-748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	36800-748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	TOP CARE (Topco Associates LLC)	36800-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (36800-748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	0363-0748-08	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Walgreens	0363-0748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (0363-0748-08) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	21130-748-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Safeway, Inc.	21130-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	80 CAPSULE, LIQUID FILLED in 1 BOTTLE (21130-748-80)	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Naproxen Sodium	0363-0748-12	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Walgreens	0363-0748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (0363-0748-12) > 120 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	0363-0748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Walgreens	0363-0748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (0363-0748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
NAPROXEN SODIUM	51013-137-28	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	PuraCap Pharmaceutical LLC	51013-137	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	03/20/2018	N/A	ANDA	1 BOTTLE in 1 CARTON (51013-137-28) > 160 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Naproxen Sodium	69842-748-08	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	CVS Pharmacy	69842-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	80 CAPSULE, LIQUID FILLED in 1 BOTTLE (69842-748-08)	N/A
Naproxen Sodium	69842-748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	CVS Pharmacy	69842-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (69842-748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	55910-748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Dolgencorp, Inc. (DOLLAR GENERAL & REXALL)	55910-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (55910-748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Naproxen Sodium	0363-0748-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	Walgreens	0363-0748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (0363-0748-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Naproxen Sodium	11673-748-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	TARGET Corporation	11673-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	1 BOTTLE, PLASTIC in 1 BOX (11673-748-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
NAPROXEN SODIUM	51013-137-15	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	PuraCap Pharmaceutical LLC	51013-137	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	03/20/2018	N/A	ANDA	1 BOTTLE in 1 CARTON (51013-137-15) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Naproxen Sodium	69842-748-16	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	ANDA208363	CVS Pharmacy	69842-748	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	04/01/2018	N/A	ANDA	160 CAPSULE, LIQUID FILLED in 1 BOTTLE (69842-748-16)	N/A
Aleve	0280-6080-16	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Bayer HealthCare LLC.	0280-6080	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/20/2007	N/A	NDA	160 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC (0280-6080-16)	N/A
Aleve	0280-6080-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Bayer HealthCare LLC.	0280-6080	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/20/2007	N/A	NDA	1 BOTTLE, PLASTIC in 1 CARTON (0280-6080-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Aleve	0280-6080-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Bayer HealthCare LLC.	0280-6080	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/20/2007	N/A	NDA	1 BOTTLE, PLASTIC in 1 CARTON (0280-6080-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Aleve	0280-6080-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Bayer HealthCare LLC.	0280-6080	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/20/2007	N/A	NDA	1 BOTTLE, PLASTIC in 1 CARTON (0280-6080-80) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Aleve	0280-6091-80	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Bayer HealthCare LLC.	0280-6091	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	02/28/2007	N/A	NDA	1 BOTTLE, PLASTIC in 1 CARTON (0280-6091-80) > 80 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
All Day Pain Relief	55319-174-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Family Dollar (FAMILY WELLNESS)	55319-174	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	12/31/2017	N/A	NDA	1 BOTTLE, PLASTIC in 1 BOX (55319-174-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
All Day Pain Relief	63940-174-40	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Harmon Stores	63940-174	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	07/31/2015	N/A	NDA	1 BOTTLE, PLASTIC in 1 BOX (63940-174-40) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A
Equate Naproxen Sodium	49035-098-27	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Wal-Mart Stores Inc	49035-098	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	08/09/2013	N/A	NDA	80 CAPSULE, LIQUID FILLED in 1 BOTTLE (49035-098-27)	N/A
Good Neighbor Pharmacy Naproxen Sodium	46122-038-58	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Amerisource Bergen	46122-038	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	01/06/2011	N/A	NDA	1 BOTTLE in 1 CARTON (46122-038-58) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Good Neighbor Pharmacy Naproxen Sodium	46122-038-60	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Amerisource Bergen	46122-038	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	01/06/2011	N/A	NDA	1 BOTTLE in 1 CARTON (46122-038-60) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Good Neighbor Pharmacy Naproxen Sodium	46122-038-65	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Amerisource Bergen	46122-038	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	01/06/2011	N/A	NDA	1 BOTTLE in 1 CARTON (46122-038-65) > 30 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description	Pharm Class
Good Neighbor Pharmacy Naproxen Sodium	46122-038-71	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Amerisource Bergen	46122-038	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	01/06/2011	N/A	NDA	1 BOTTLE in 1 CARTON (46122-038-71) > 50 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Leader Naproxen Sodium	37205-854-58	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Cardinal Health	37205-854	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	12/01/2010	N/A	NDA	1 BOTTLE in 1 CARTON (37205-854-58) > 40 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Leader Naproxen Sodium	37205-854-60	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Cardinal Health	37205-854	Naproxen sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	12/01/2010	N/A	NDA	1 BOTTLE in 1 CARTON (37205-854-60) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE	N/A
Naproxen Sodium	41520-075-20	220 mg/1	CAPSULE, LIQUID FILLED	ORAL	NDA021920	Care One (American Sales Company)	41520-075	Naproxen Sodium	NAPROXEN SODIUM	HUMAN OTC DRUG	10/31/2014	N/A	NDA	1 BOTTLE, PLASTIC in 1 BOX (41520-075-20) > 20 CAPSULE, LIQUID FILLED in 1 BOTTLE, PLASTIC	N/A

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Background Information (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

Drug questions email: **DRUGINFO@FDA.HHS.GOV (mailto:DRUGINFO@FDA.HHS.Gov)**

See also: **Drug Registration and Listing Instructions (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm)**
National Drug Code Directory Data Files (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

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